An Efficient Conversion of Diosgenin into 22-Oxocholesterol

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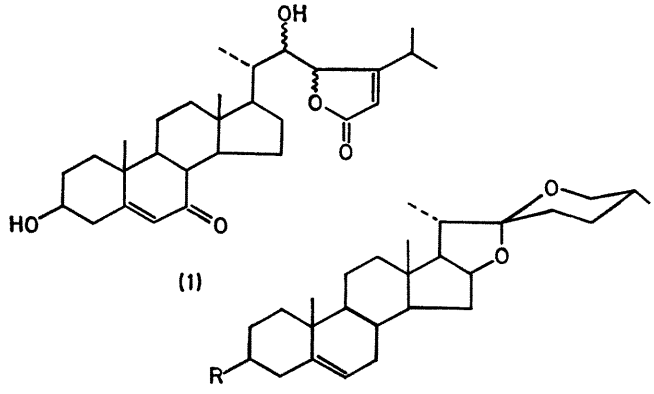
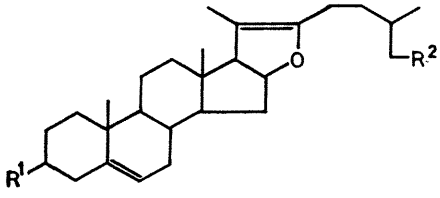
Summary Diosgenin has been converted in 50% overall yield into a 1 : 1 mixture of 20*S*- and 20*R*-22-oxocholesterols, from which the 20*S*-22-ketone (containing the natural stereochemistry at C-20) can be isolated in good yield *via* a repeated equilibration procedure.

WITH the appearance of the structure elucidation[1] and synthesis[2] of antheridiol (**1**) (the first steroidal sex hormone to be recognized in the plant kingdom), the increasing

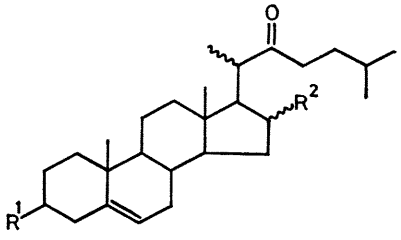


(1)

(2) R = OH
(3) R = OAc



(4) $R^1 = R^2 = OAc$
(5) $R^1 = R^2 = OH$
(6) $R^1 = R^2 = OTs$
(7) $R^1 = OH$, $R^2 = OTs$
(8) $R^1 = OH$, $R^2 = H$



(9) $R^1 = OH$, $R^2 = Br$
(10) $R^1 = OH$, $R^2 = H$, 20 *S*
(11) $R^1 = OH$, $R^2 = H$, 20 *R*
(12) $R^1 = OAc$, $R^2 = H$, 20 *S*
(13) $R^1 = OAc$, $R^2 = H$, 20 *R*

volume of knowledge in the ecdysones[3] and the mode of action of vitamin D,[4] the growing importance of side chain functionalized C_{27} and C_{29} sterols became apparent. We therefore sought a cheap route to such compounds, and now report the efficient conversion of diosgenin (**2**) into 22-oxocholesterol.

Diosgenin acetate (**3**) was heated under reflux for 45 min in ethylene glycol diacetate as solvent, in the presence of pyridine (1 equiv.), acetyl chloride (1 equiv.), methylamine hydrochloride (1·1 equiv.), and acetic anhydride (4·5 equiv.), to give pseudodiosgenin diacetate (**4**), which was then hydrolysed by sodium bicarbonate in aqueous methanol under reflux to give pseudodiosgenin (**5**) in 97% yield from (**3**). The yield is slightly greater than that obtained by patented procedures.[5] The diol (**5**) was added to tosyl chloride (4 mol) in pyridine and the ditosylate[6] (**6**) isolated after 4 h in 83% yield. The ditosylate (**6**) was hydrolysed to the monotosylate (**7**)[6] in 3 : 1 acetone–water under reflux for 3 h, and (**7**) reduced with $LiAlH_4$ in tetrahydrofuran to give 26-deoxypseudodiosgenin (**8**) (m.p. 142—143°) in 80% yield from (**6**). Initial attempts to convert the dihydrofuran (**8**) into a 22-ketone functionalised at C-16 were unsuccessful; treatment of (**8**) with formic acid–dimethylformamide failed to give the 22-oxo-3,16-diformate, producing instead specific reduction of the $\Delta^{20(22)}$-bond in 80% yield. However, when a solution of (**8**) in methylene chloride was stirred in a 2-phase system for 6 h with 48% aqueous hydrogen bromide moderated with an equal volume of lithium bromide–water (w : w 1 : 1), a crude and unstable bromoketone (**9**) was obtained (ν_{max} 1705 cm^{-1}), which was directly reduced with a zinc–copper couple in aqueous ethanol to a product containing 60% of a mixture of 20*S*-22-oxocholesterol (**10**) and 20*R*-22-oxocholesterol (**11**) (the former containing the natural stereochemistry at C-20). When this crude product was recycled twice through the HBr–LiBr and Zn–Cu couple treatments, the final product contained 95% of a mixture of (**10**) and (**11**) in the ratio *ca.* 1 : 6. This mixture was acetylated (acetic anhydride–pyridine) to give, after crystallisation of the product, 20*R*-22-oxocholesteryl acetate (**13**) contaminated with *ca.* 10% of the known 20*S*-22-oxocholesteryl acetate (**12**)[7] from which it could not readily be separated.

When the mixture of (**10**) and (**11**) obtained *via* the recycling procedure from (**8**) was subjected to base-catalysed equilibration (12% sodium methoxide in A.R. methanol, 24 h under reflux) and subsequently acetylated, a 1 : 1 mixture of the 20*S*- and 20*R*-22-oxo-3β-acetates (**12**) and (**13**) was obtained. Repeated crystallisation of this mixture from ethanol gave pure (**12**), identical in all respects with material synthesised *via* the procedure of Cole and Julian.[7]

If the sequence from diosgenin (**2**) to the 1 : 1 mixture of 20*S*- and 20*R*-22-oxo-cholesterols is carried out with greatest efficiency (in terms of overall yield of these products), the overall yield is *ca.* 50%. In large scale recrystallisations of the 1 : 1 mixture (50 g) of (**12**) and (**13**), followed by re-equilibration of the mother liquors, as described, and further recrystallisations, 20*S*-22-oxocholesteryl acetate (**12**) (25 g), containing not more than 5% of (**13**) as contaminant, could be isolated without difficulty. In further experiments, the 20*S*-22-ketone has been selectively brominated at C-23 and dehydrobrominated to the corresponding 23-en-22-one system; Michael addition of the malonate anion to this $\alpha\beta$-unsaturated ketone has been successfully carried out, thus providing an entry to the sitosterol skeleton.

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